To Understand, Prevent and Heal the Effects of Stress

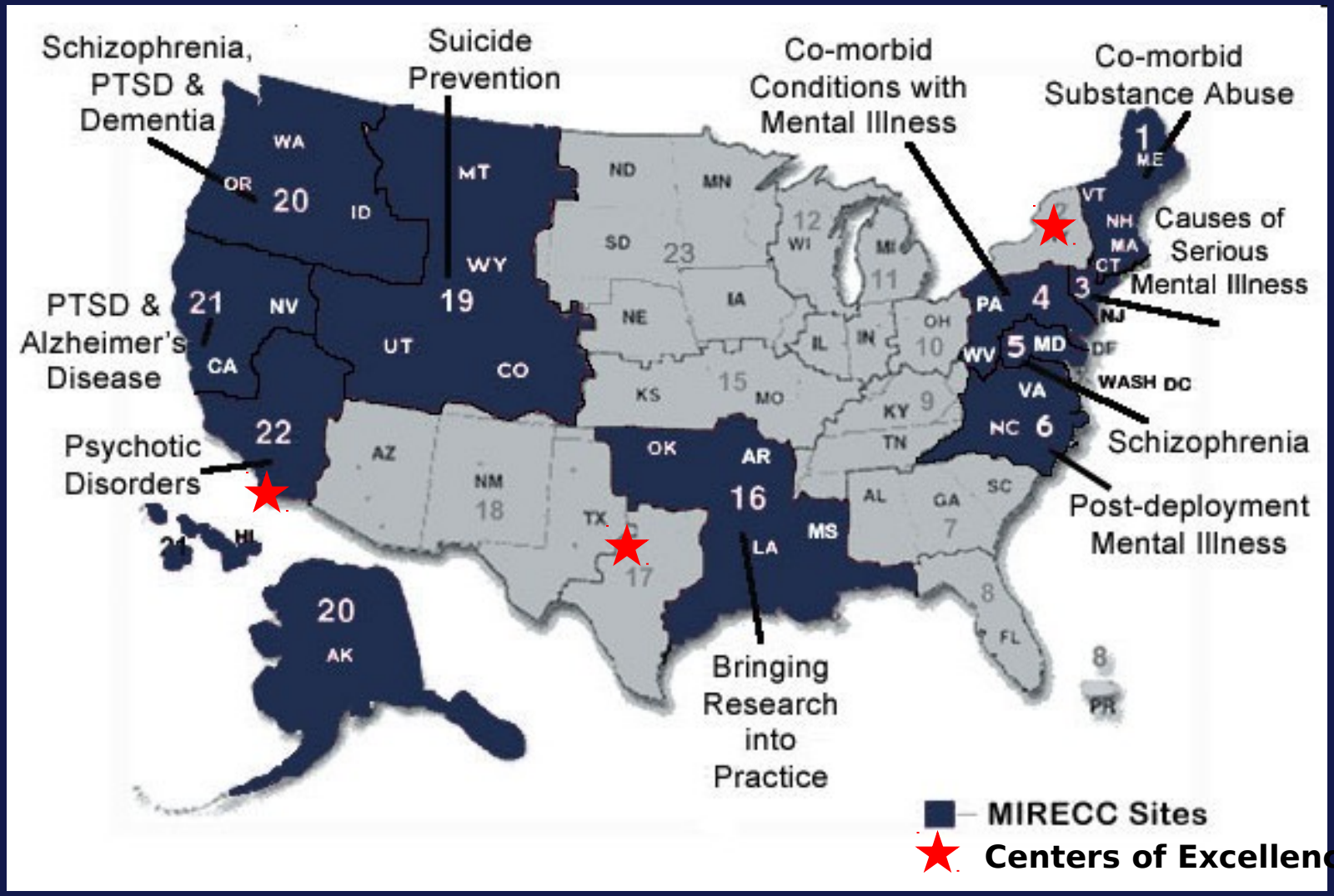
James Lohr, M.D. - Director

Laurie Lindamer, Ph.D. - Director of Education

Dewleen Baker, M.D. - Director of Research

Niloo Afari, Ph.D. - Director of Clinical

MIRECCs and COEs



CESAMH Vision

Through clinical and translational research, innovative therapeutic programs, and education and training, to be a national resource for cutting-edge understanding and state-of-the-art treatment of stress- and trauma-related problems.

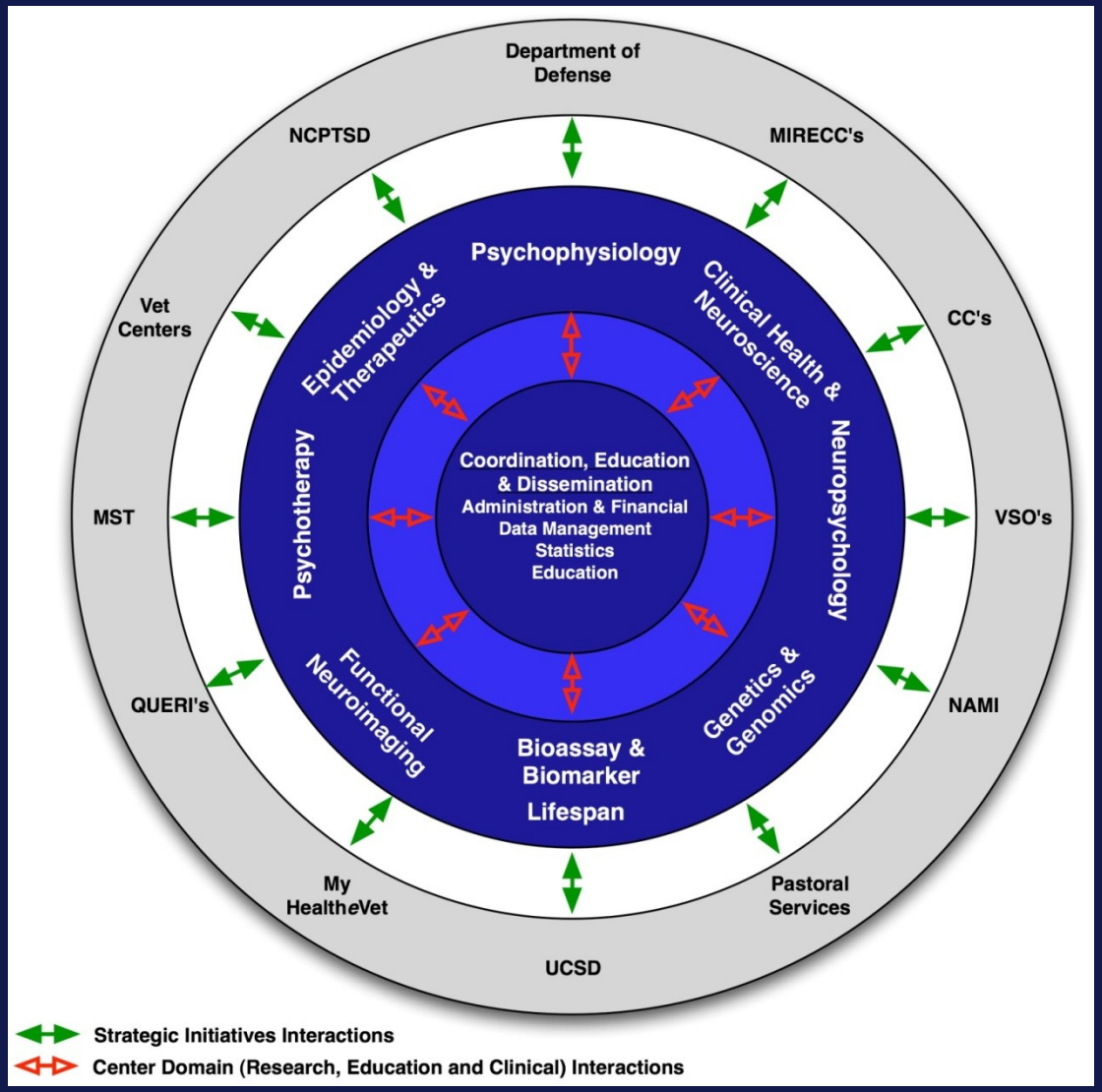
Center Focus

- The effects of stress in the Operation Iraqi Freedom (OIF)/ Operation Enduring Freedom (OEF) contingents and veterans.
- Post-traumatic stress disorder (PTSD).
- The mental health concomitants of traumatic brain injury (TBI).
- The interaction of physical and mental health consequences of stress exposure.

Functional Units

- Coordination, Education, and Dissemination Unit (J. Lohr, L. Lindamer, C. Rodgers and M. Frybarger)
- Clinical Health and Neuroscience Unit (D. Baker, N. Afari and T. Moeller-Bertram)
- Epidemiology, Genomics and Therapeutics Unit (J. Lohr, M. Tsuang and C. Nievergelt)
- Functional Neuroimaging Unit (M. Paulus and A. Simmons)
- Stress and Pain Unit (I. Strigo and T. Moeller-Bertram)
- Lifespan Unit (W. Kremen and S. Ancoli-Israel)
- Neuropsychology Unit (D. Delis, A. Jak and B. Twamley)
- Psychophysiology Unit (V. Risbrough and M. Geyer)
- Psychotherapy Unit (A. Lang, S. Thorp and S. Norman)
- Bioassay and Biomarker Unit (R. Kuczenski and R. Hauger)

CESAMH Collaboration



Clinical Activities

- Planned development of the Women's Combat PTSD program (with Naval Medical Center San Diego)
- VISN-22 Clinical Assessment for Reintegration and Enrollment (CARE) in Veterans Transition Centers
- Peritraumatic Behavior Questionnaire for assessment of embedded personnel (in collaboration with DOD (W. Nash, Navy & Marine Corps)

Education Activities

- **Training in Evidence-Based Practices**
  - VA, DoD, Vet Centers, Community Providers
  - Prolonged Exposure Therapy (n=60)
  - Cognitive Processing Therapy (>200)
  - Implementation of CPT CE course
- **Dissemination**
  - Publication in scientific journals
  - National Newsletter
  - Education for Probation and Police Departments about incarcerated veterans
  - Educational seminars for veterans with TBI
- **Collaboration and communication both within the CESAMH and other relevant agencies**
  - Community Advisory Board
  - MIRECCs, other CoEs

Research in CESAMH

- CESAMH provides infrastructure for research studies
- CESAMH provides salary support for researchers
- CESAMH provides opportunities for interactions between CESAMH researchers and the DOD
- CESAMH provides for translational research collaborations

Collaborations with DOD

- Funding through the new CDMRP mechanisms

Other active research collaborations include

- Naval Health Research Center
- Naval Center Combat and Operational Stress Control
- Marine Corps
- INTRUST (Army, Ft. Detrick)

VISN-22 CESAMH: PTSD Research Activities

Major Clinical Research Studies, collaborations with DOD

- Marine Resiliency Study (Marines), funded by VAHSR&D, USMC, and Navy BUMED
  - This study evaluates two battalions of Marines pre- and post-deployment to determine genetic, physiological, and neuropsychological factors related to resiliency to the development of PTSD
- Validation of the Peritraumatic Behavior Questionnaire-Observer Rated, funded by CDMRP
  - The PBQ is an instrument for assessment of embedded personnel to assess in-theater risk for combat PTSD Marines
- Telemedicine for Evidence-Based Psychotherapies, funded by VA and by VA and CDMRP
  - These are studies of the use of telemedicine to deliver PE and CPT treatment for PTSD
- Pain Perception and PTSD, funded by FAER
- Alcohol Use Disorder and PTSD Treatment in Victims of Partner Violence, funded by NIH
- Using fMRI to Measure Brain Response to Exposure-Based Psychotherapy in Individuals with Combat-Related PTSD, funded by CDMRP

VISN-22 CESAMH: PTSD Research Activities

We are a site for the following Multisite Studies

- **Nepicastat for PTSD, funded by CDMRP**
- **Ganaloxone for PTSD, funded by the Consortium for Psychological Health and Traumatic Brain Injury (Injury, Stress, and Trauma, INTRUST)**
- **Multisite Study of CBT for PTSD, funded by Navy BUMED (in collaboration with the NCPTSD)**
- **VA Cooperative Study #519 Genetic Tissue Banking for Integrating Practice Guidelines for Smoking Cessation into Mental Health Care for PTSD (funded by the VA)**

VISN-22 CESAMH: PTSD Research Activities

Major Basic Studies into Stress Mechanisms

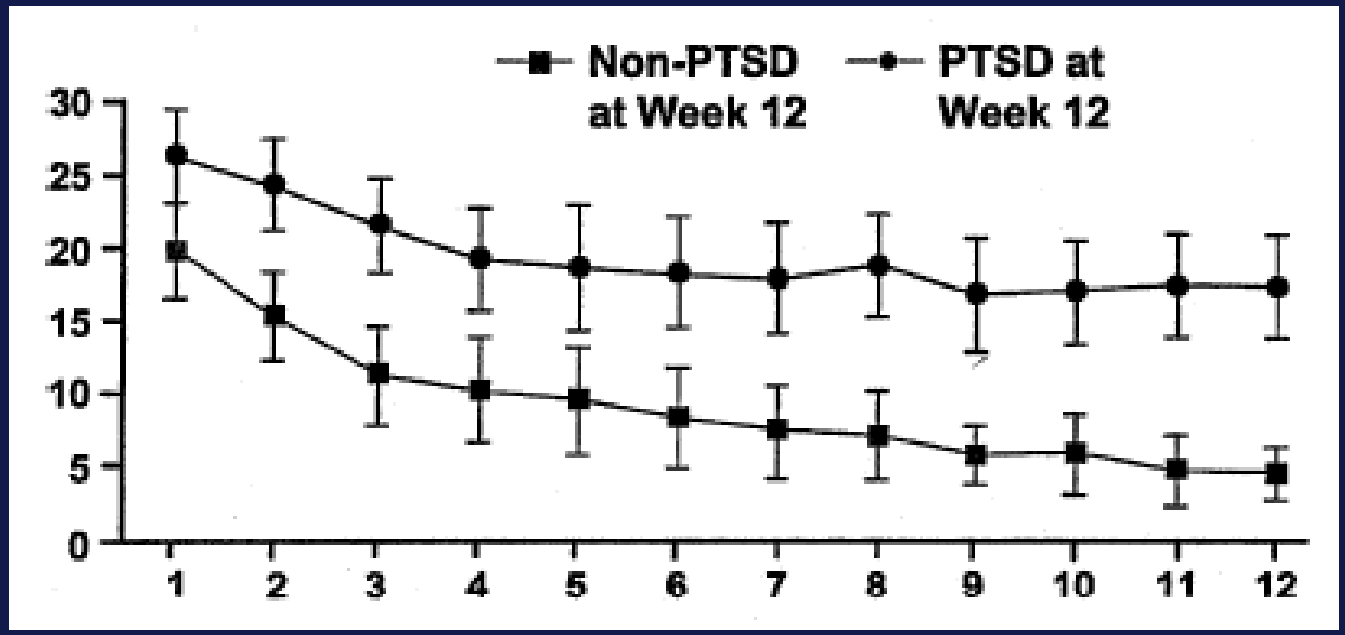
- CRF-R1 ERK Signaling and Mediation of Stress and Startle Hyperreactivity, funded by VA
- Assessing Fear Extinction via Startle, funded by VA and CDMRP
- Understanding the Role of COMT Variants in Sensorimotor Gating, funded by NIH
- Understanding neurobiological mechanisms underlying Pain and PTSD, funded by FAER

Examples of Translational Research in CESAMH

Corticotropin releasing factor in PTSD
Victoria Risbrough Ph.D.

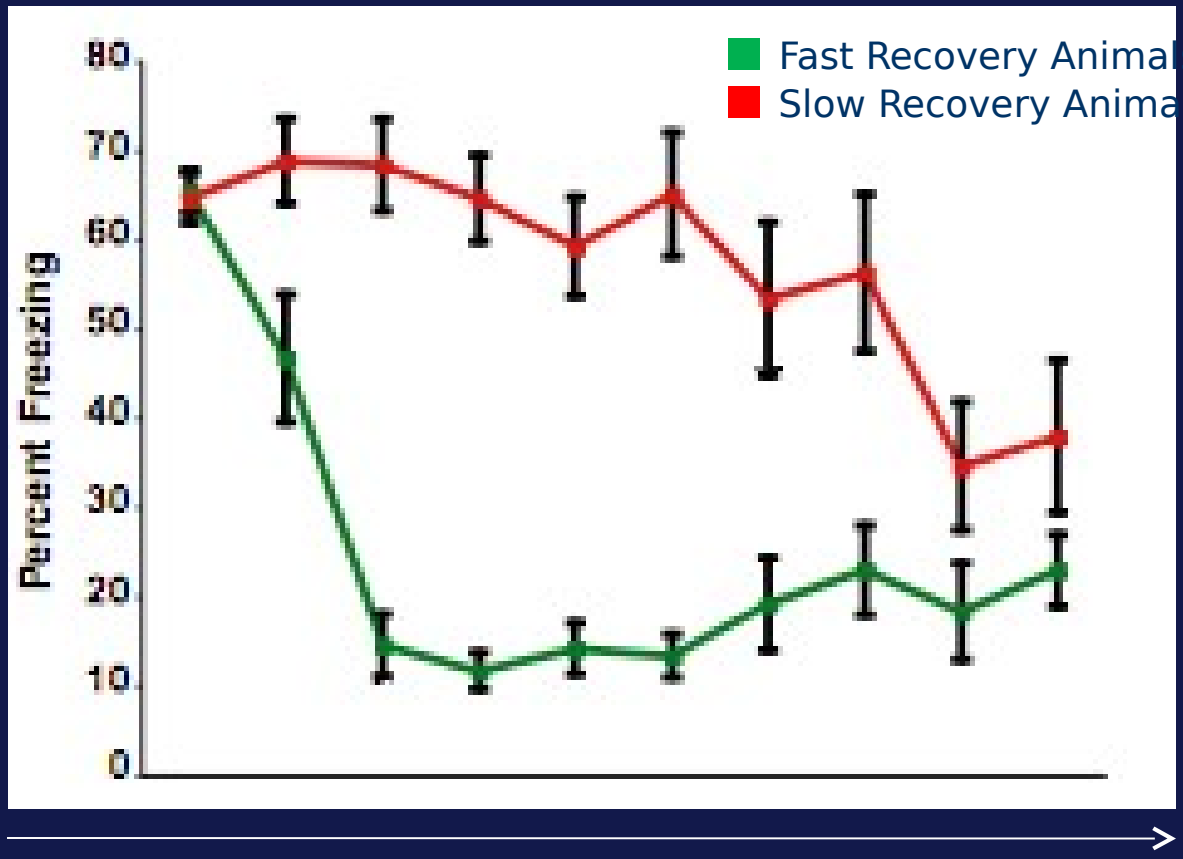
Neuropeptide Y in risk and resilience for PTSD
Dewleen Baker M.D.

Extant hypothesis: PTSD is due to a failure in fear recovery mechanisms



Rothbaum and Davis, 200

Using a mouse model to test the hypothesis that individual variance in NPY signaling predicts fear recovery from trauma



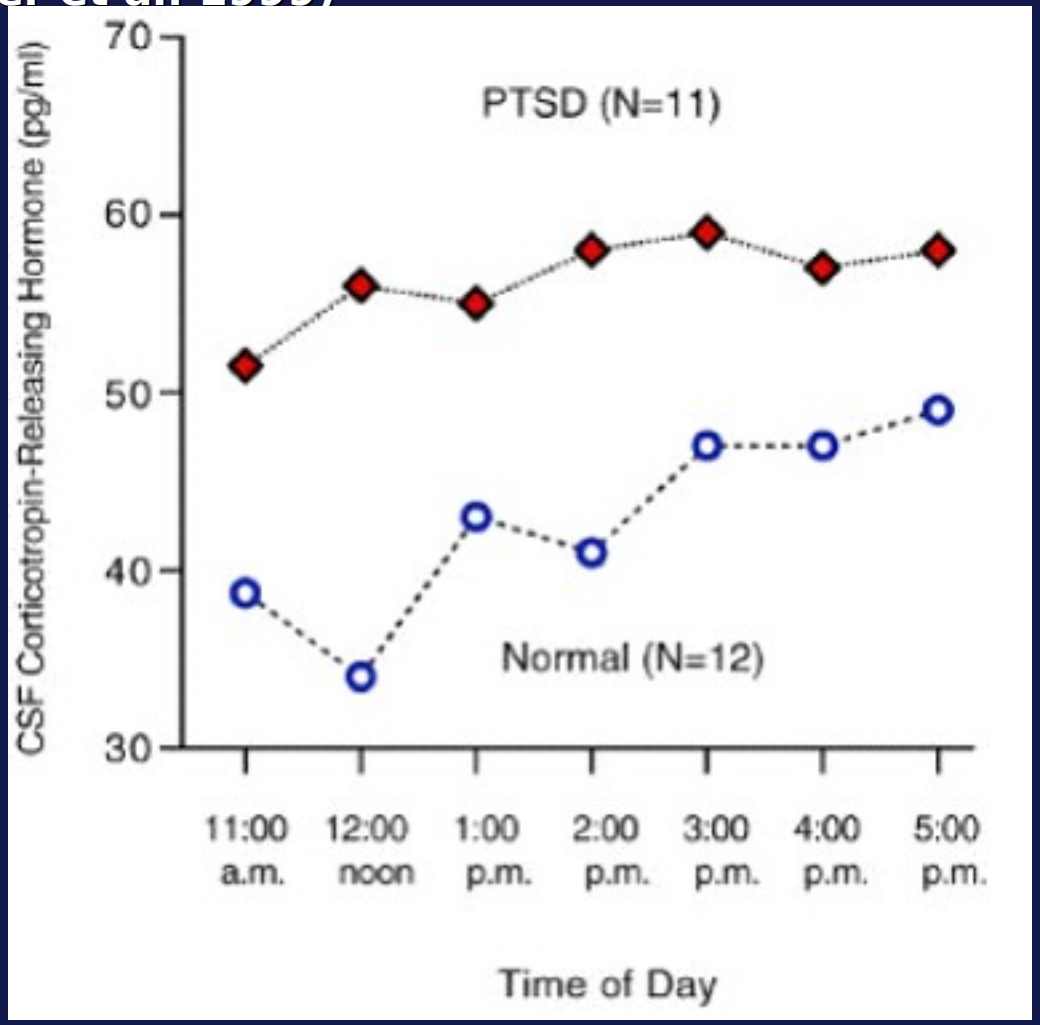
Aim 1: Analysis of NPY expression and signaling pre and post trauma.

Aim 2: Does increasing NPY expression facilitate slow learner recovery?

Perez NIH NRSA Application

Corticotropin Releasing Factor

- **Hypersecretion of CRF is exhibited in PTSD and depression** (e.g. Holsboer et al 1986, Nemeroff et al 1984, Bremner et al 1997, Baker et al. 1999)

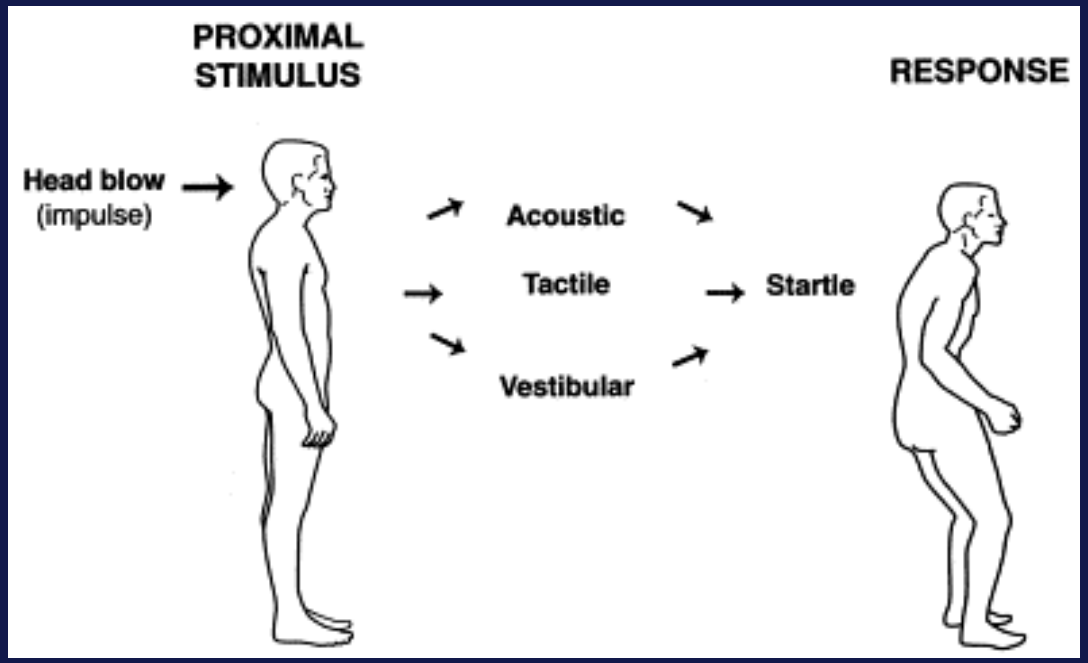


Broad Questions:

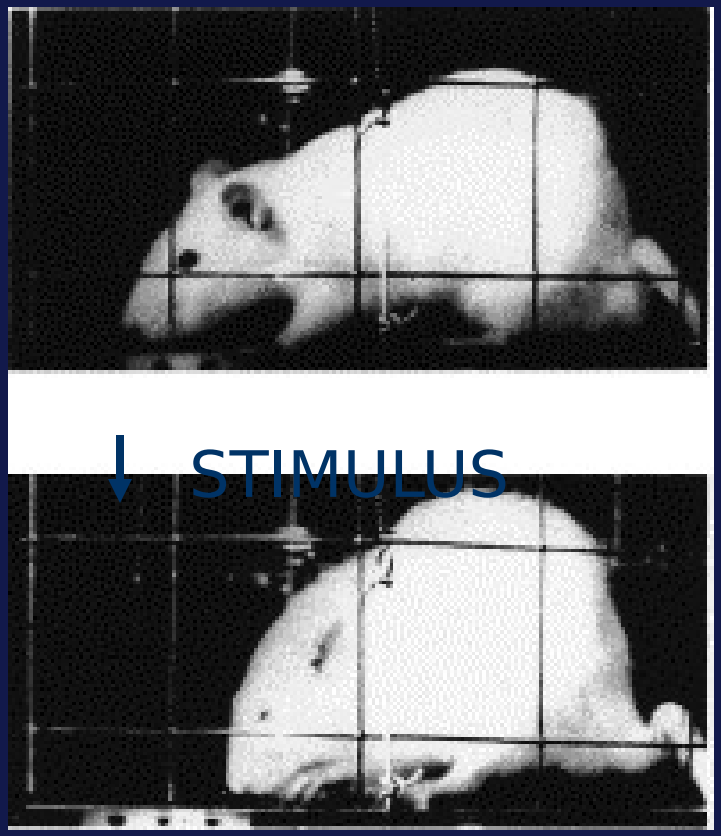
- Does CRF play a role in PTSD symptoms?
- Is increased CRF a vulnerability factor for development of PTSD or does it occur only after trauma exposure in PTSD subjects?
- What is the mechanism of CRF effects on stress responses?
- What are areas of potential efficacy for drugs targeting CRF – prophylactic or therapeutic?

Acoustic Startle Reflex

- Acoustic startle reflex: a contraction of the skeletal musculature in response to a high intensity acoustic stimulus.
- Postulated function: Defensive mechanism for protection from immediate attack.
- Exaggerated startle a hallmark symptom of combat related PTSD



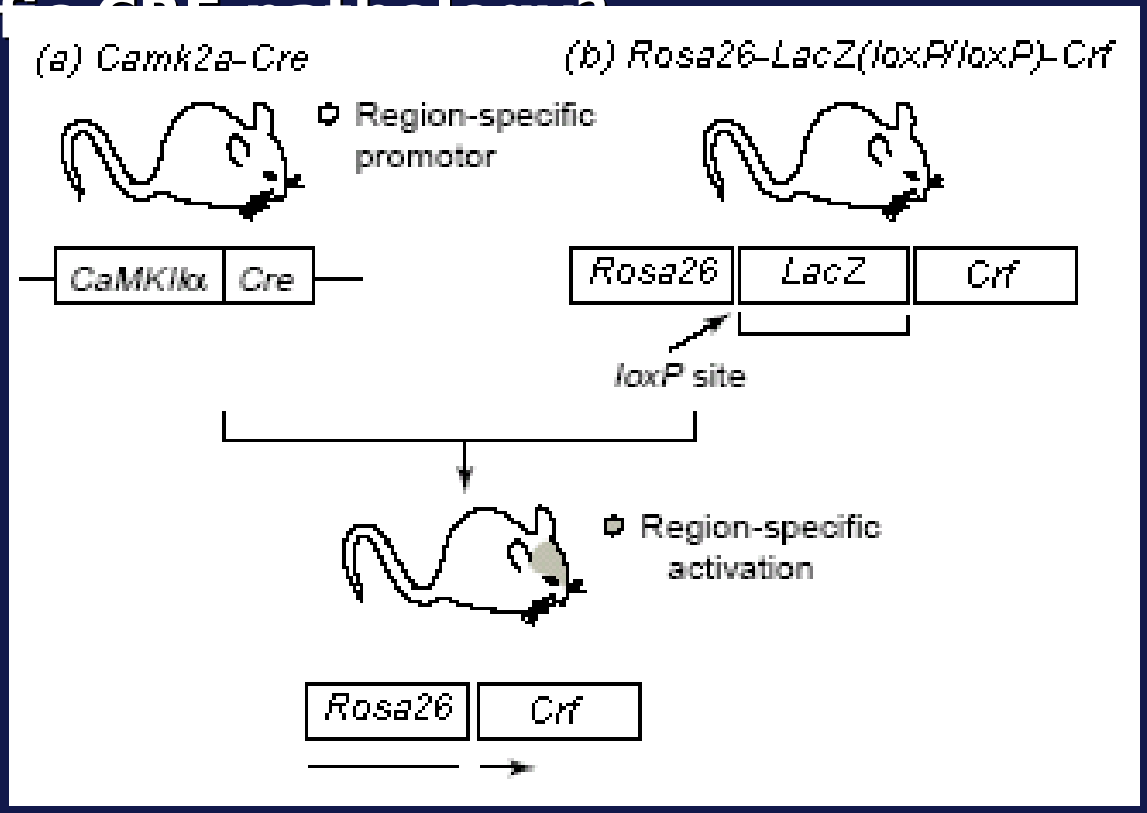
Yeomans et al. 2002



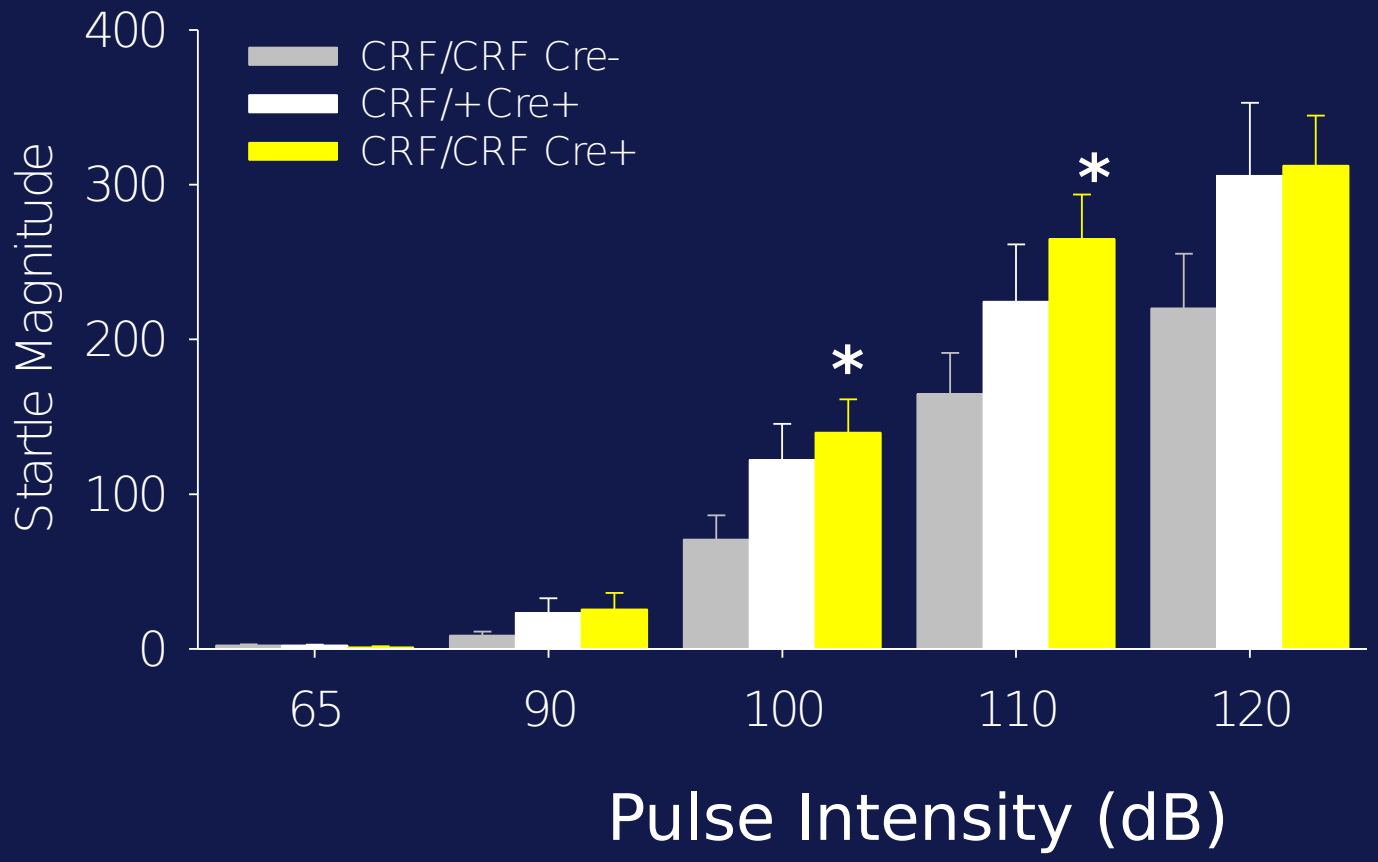
Adapted from Horlington 1970

Modeling chronic CRF effects on startle via targeted overexpression

- PTSD patients exhibit increased CRF concentrations in CSF (Baker et al 1999; Bremner et al 1997).
- Can CRF-overexpression model aspects of this specific CRF pathology?

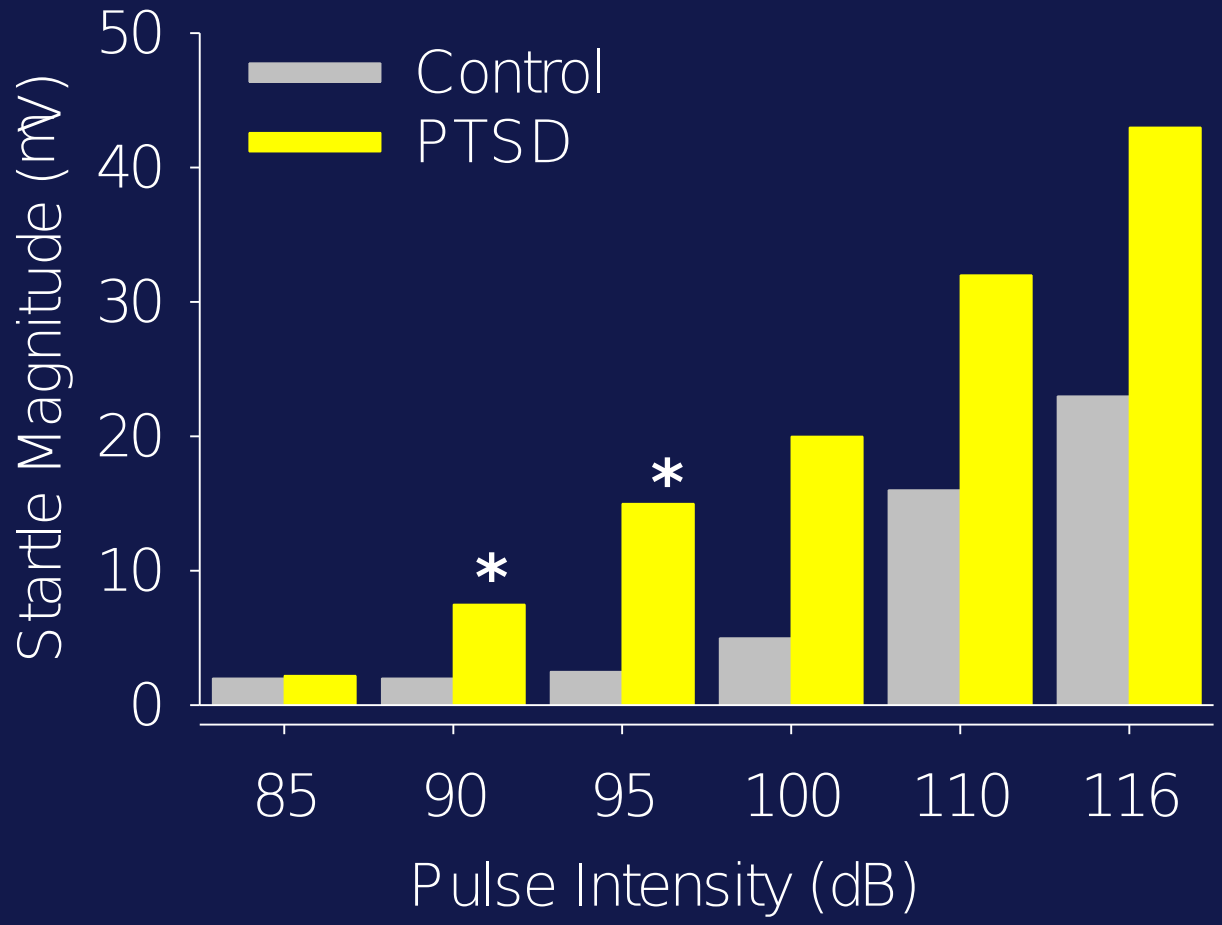


Neuronal CRF-overexpression induces increased startle reactivity in mice



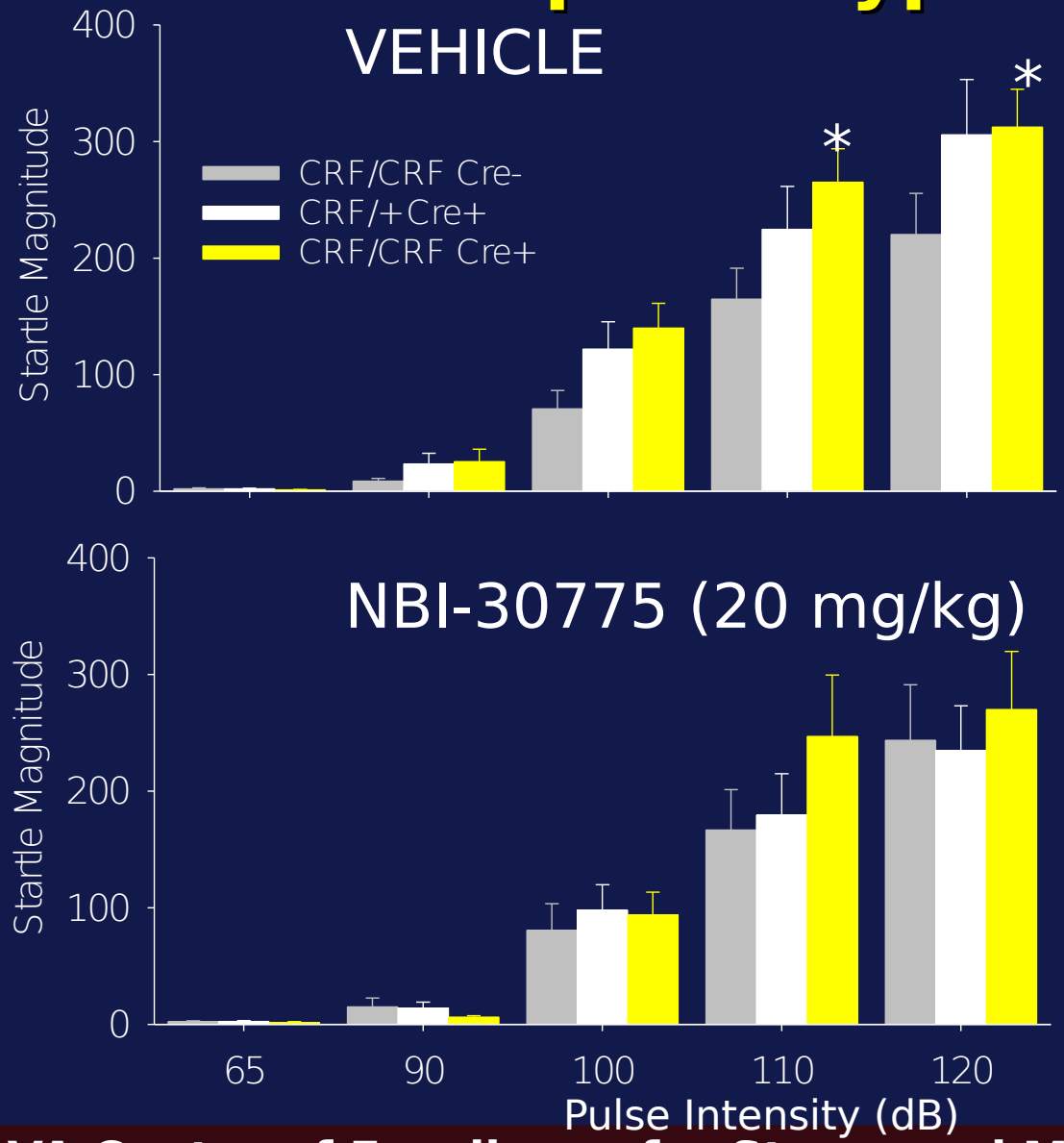
*p<0.05 vs. CRF/CRF Cre-

Increased startle in PTSD



From Butler et al. 1990

CRF_1 blockade attenuates CRFOE startle phenotype



*p<0.05 vs. CRF/CRF Cre

Modeling CRF contribution to trauma effects on enduring anxiety: Adamec predator stress test

10 min exposure to predator

-2 days

0

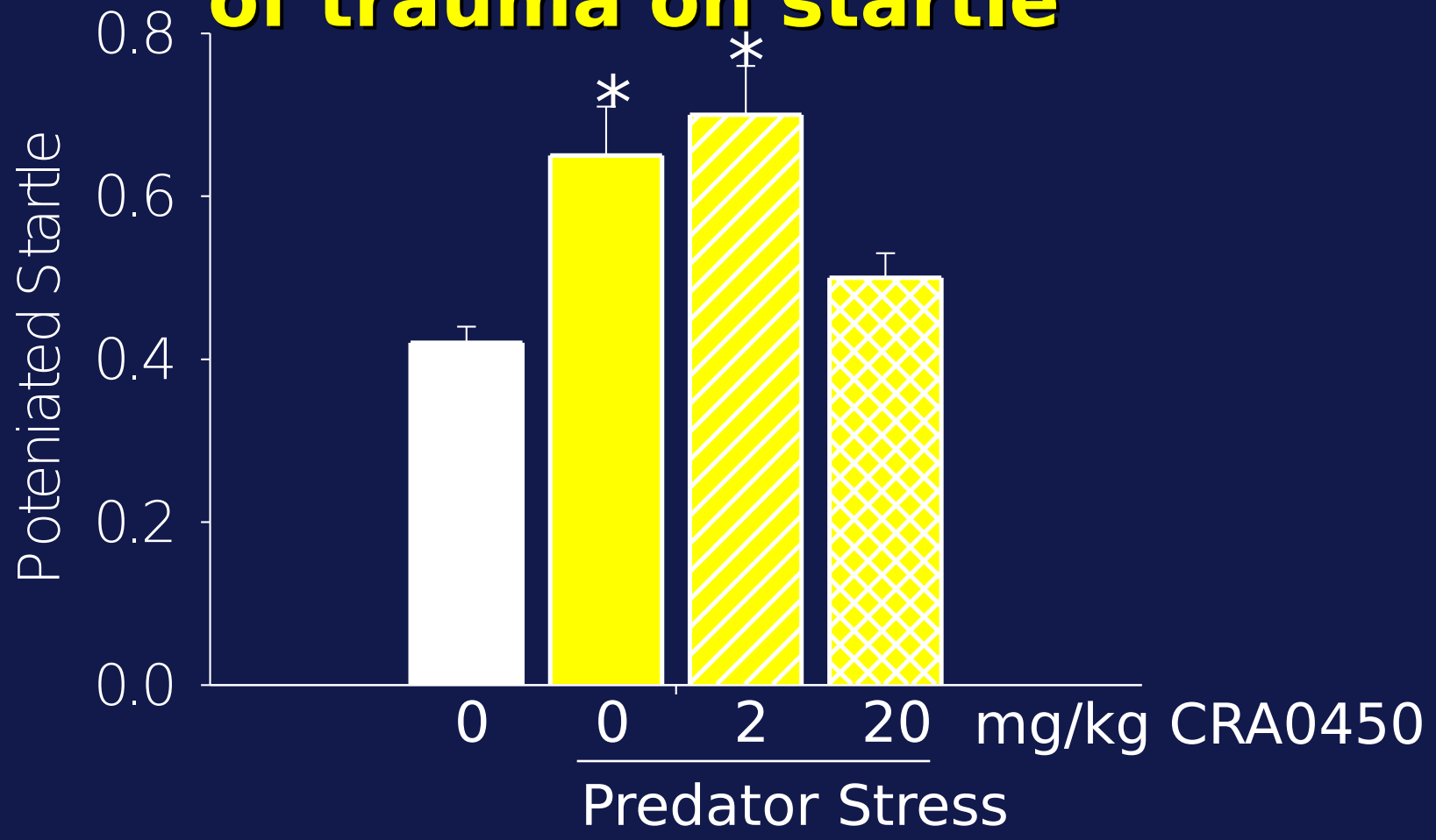
10 days

CRA0450
CRF_1 antagonist, IP

Pre-stress startle test

Post-stress startle tes

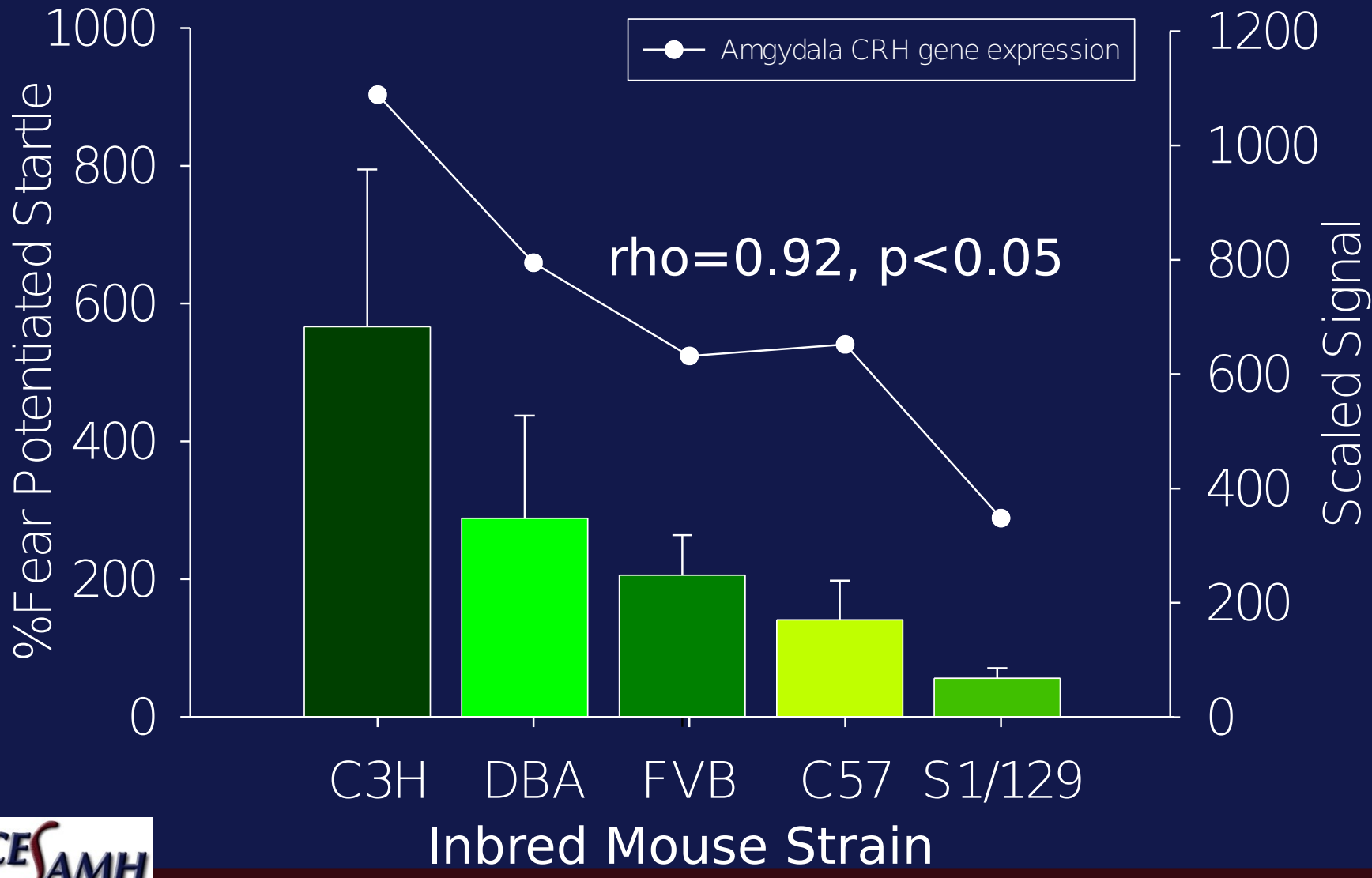
CRF_1 receptor blockade may be prophylactic against enduring effects of trauma on startle

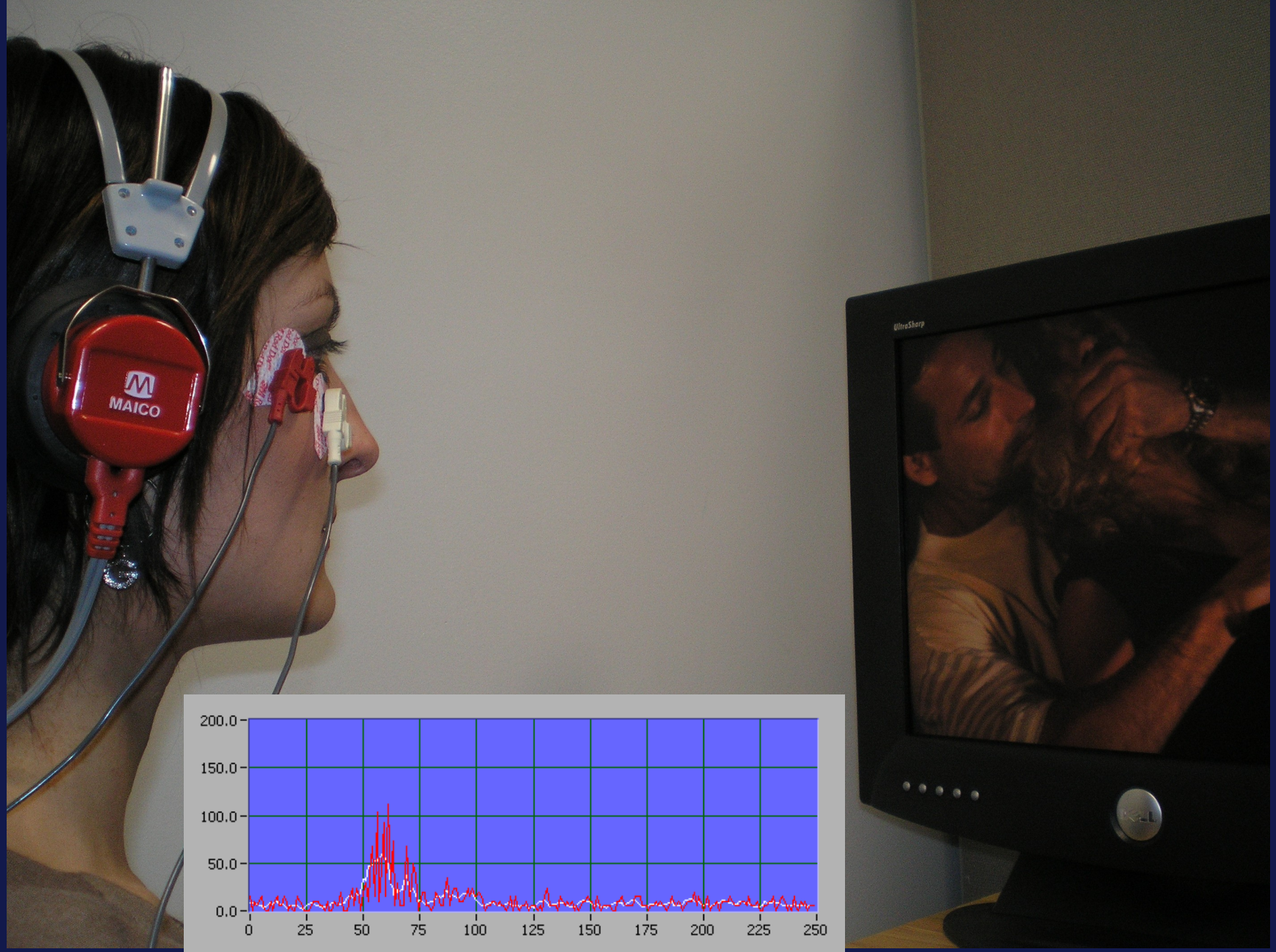


Adamec, Fougere, Risbrough 2009

*p<0.01 vs. No Stress control

Heritable variance in CRF gene expression in amygdala predicts fear-potentiated startle





Trial Type pr

Coded Information 1213 , 2 , 12 ,

V Start	V Max	T Max	Average	Base Line	Onset	T Peak 1	Amp Peak 1
8	64	59	11	7	34	59	59

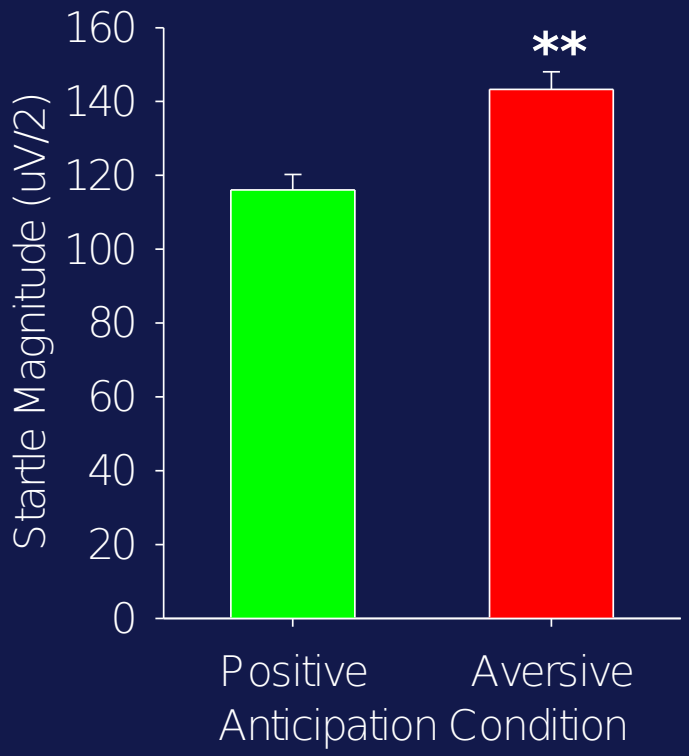
CESAMH

V and Mental Health

Fear Potentiated Startl

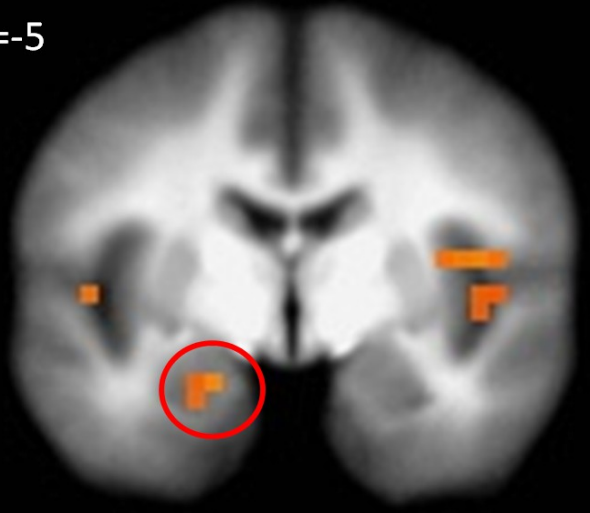
Cue alerts subject to oncoming stimulus – pleasant or aversive

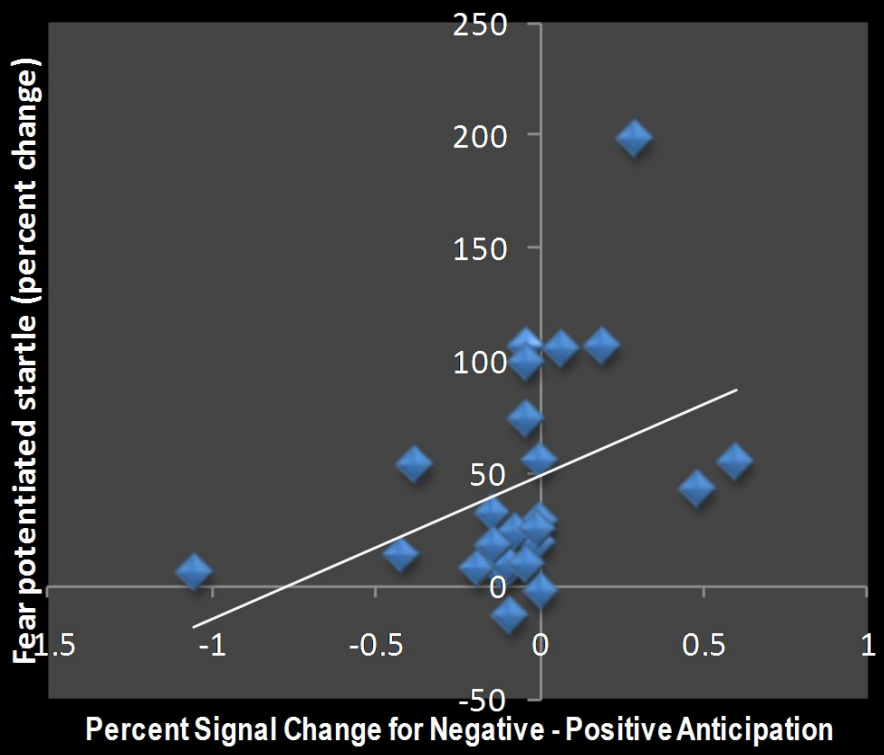
Startle recorded during anticipation

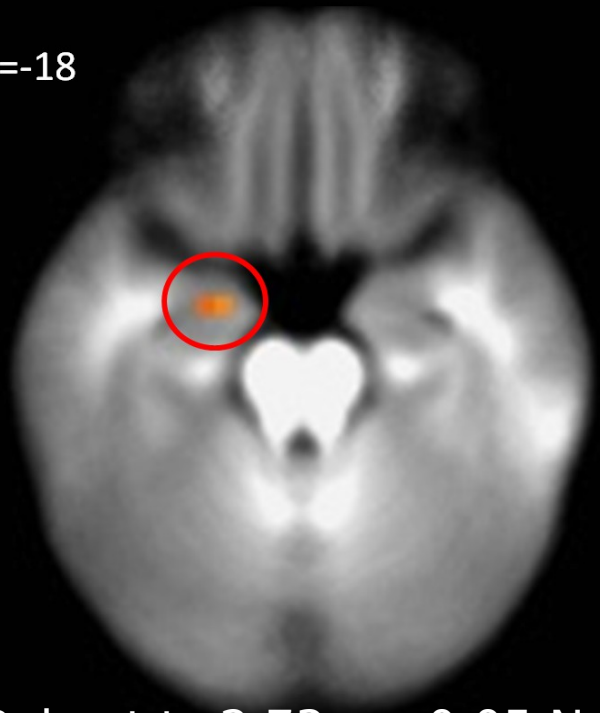


**t 106 = -13, P<

FPS responding is linked to amygdala activation

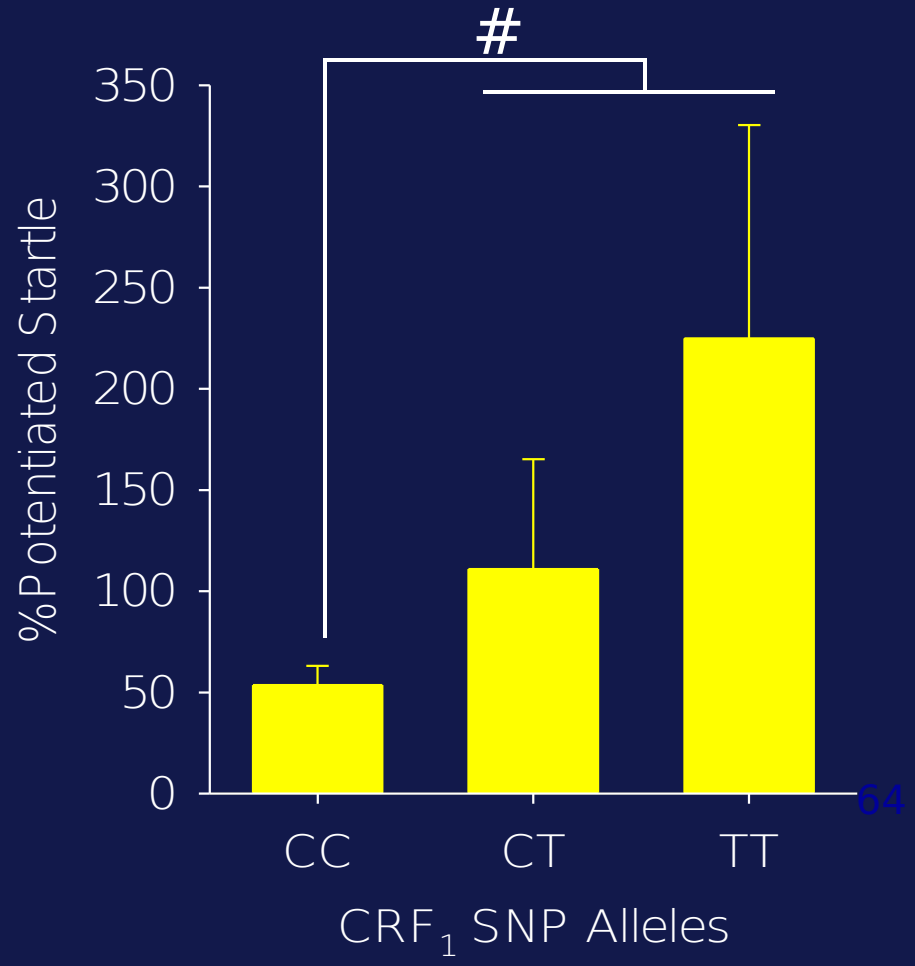






Robust t=2.73, p<0.05 N=25

FPS may be sensitive to genetic variance in CRF_1



*CRF_1 gene SNP Rs4792887 r=.313, p<0.005, N=78

CC vs. T carrier t(76)=-2.5, p<0.008

Examples of Translational Research in CESAMH

Neuropeptide Y

- Basic animal model – Geyer/Risbrough lab
- Serial Cerebrospinal Fluid Studies of PTSD , funded by VA
- Marine Resiliency Study, funded by VAHSR&D, Marine Corps & Navy BUMED

- Goals:
  - To better understand the relationship between Peripheral (blood) and Central (cerebrospinal fluid) NPY concentrations and risk/resilience to combat stress
  - To determine the impact of NPY concentrations on physical (blood pressure) and mental health (PTSD) manifestations of stress
  - Using a prospective, longitudinal design, determine the impact of peripheral concentrations (blood) of NPY on risk for PTSD in Marines deployed to combat

Summary

CESAMH resources are directed toward clinical, education and research activities

CESAMH has multiple collaborations, including with DOD

The multidisciplinary nature of the center placed the center in a unique position to do translational research